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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/527,346 | 09/23/2005 | Fabrice Le Gall | 03528.0146.PCUS00 | 7228 |

27194 7590 07/09/2009

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| EXAMINER | |
|---|---|
| SKELDING, ZACHARY S | |
| ART UNIT | PAPER NUMBER |
| 1644 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 07/09/2009 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/527,346 | LE GALL ET AL. | |
| | Examiner | Art Unit | |
| | ZACHARY SKELDING | 1644 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *27 March 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-7 and 13-25* is/are pending in the application.

4a) Of the above claim(s) *3,4 and 14-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5-7,13 and 18-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**DETAILED ACTION**

1. Applicant's remarks and amendments filed March 27, 2009 are acknowledged.

   Claims 1-7 and 13-25 are pending.

   Claims 1 and 5-7 have been amended.

   Claims 8-12 have been canceled.

   Claims 21-25 have been added.

   Claims 1, 2, 5-7, 13 and 18-25 are under examination as they encompass human anti-CD3 antibodies having certain characteristics wherein the elected species of antibody is an antibody which is the product of non-covalent dimerization or multimerization of single chain Fv antibodies wherein the antibody comprises two or more scFv antibodies wherein the Vh and Vl domains of each scFv are separated by peptide linkers or by no linkers in an orientation preventing their intramolecular pairing, i.e., the diabody format.

   Claims 3, 4 and 14-17 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Group or species of invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on June 6, 2008.

2. This Office Action is in response to applicant's remarks and amendments filed March 27, 2009.

   The prior rejections of record can be found in the Office Action mailed October 3, 2008.

   The previous rejection under 35 USC 112, 1st and 2nd paragraphs and 35 USC 102(e) have been withdrawn in view of applicant's amendment to the claims.

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

   (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. Claims 1, 2, 6, 13 and 18-20 stand rejected and new claims 21, 23 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith et al. (WO 9847531) in view of Hsu et al. (Transplantation. 1999 Aug 27;68(4):545-54), Holliger et al. (5,837,242) and Chapman et al.

(Nat Biotechnol. 1999 Aug;17(8):780-3), for the reasons of record as put forth in the prior Office Action mailed October 3, 2008.

Applicant argues that one of ordinary skill in the art would not have been motivated to make the claimed antibodies in view of the reference teachings. Applicant further argues the claimed antibodies have unexpected properties relative to "the parental antibody." Lastly applicant argues Holliger teaches away from the claimed invention.

Applicant's arguments have been considered but have not been found convincing, for the reasons of record as put forth in the Office Action mailed October 3, 2008 and as discussed below.

With respect to motivation to combine, applicant argues "Although Smith et al. teach that F(ab')2 were inappropriate for clinical use due to small available quantities, reduced serum half-life and contamination with whole mAb, Smith et al. do not indicate that the drawbacks of F(ab')2 are related with the constant CL and CH1 domains of Fab-fragments....Smith et al. do not provide any suggestion to make a diabody devoid of constant domains." Along these same lines applicant argues "although Smith et al. teach that F(ab ')2, which are a large portion of a whole antibody, can be immunosuppressant, this would not have made obvious that synthetic diabodies having a different and rigid structure compared to F(ab')2 may be an immunosuppressant in the same way."

Applicant's argument is not found convincing because essentially as put forth in the previous Office Action the teachings of Smith that "the production of $F(ab')_2$ fragments in large quantities remains difficult" and "recent studies have shown that even a small contaminant of whole mAb in the F(ab') preparation ($<1/10^4$ molecules) has a synergistic effect on T cell activation" do provide motivation for the skilled artisan to identify an alternative to anti-CD3 $F(ab')_2$ fragments, and the diabody is one such alternative. As stated in the previous Office Action, "One of ordinary skill in the art would have been motivated to make an anti-CD3 diabody in particular because, unlike the bivalent anti-CD3 $F(ab')_2$, the bivalent anti-CD3 diabody does not run the risk of being contaminated with intact antibodies. Furthermore, given that large-scale cost efficient production is possible with Fab', Fv and scFv according to Chapman, one of ordinary skill in the art, filtered through their knowledge of the art, would readily surmise that large-scale cost efficient production of a diabody would also be reasonable, in contrast to the teachings of Smith regarding the difficulty of producing large quantities of $F(ab')_2$ fragments."

With respect to applicant's argument that it would not have been obvious to one of ordinary skill in the art that "synthetic diabodies having a different and rigid structure compared to F(ab')2 may be an immunosuppressant in the same way," applicant has not provided objective evidence or sound scientific reasoning in support of their assertion, and arguments of counsel cannot take the place of factually supported objective evidence, see MPEP § 2145. In contrast, as taught by Smith, bivalent but FcR-nonbinding anti-CD3 antibodies immunomodulate the Th1/Th2 cytokine balance in favor of Th2 by inducing a partial signal

upon CD3 crosslinking (see, e.g., Smith page 2, 2nd paragraph; page 16 and page 18, 2nd paragraph). There is no a priori reason to believe that a bivalent but FcR-nonbinding anti-CD3 diabody would fail to "be an immunosuppressant in the same way" as argued by applicant.

Turning to applicant's argument that the claimed antibodies have unexpected properties relative to "the parental antibody," this is also not found convincing.

In comparing an OKT3 derived anti-CD3 diabody to full length OKT3 applicant fails to compare the claimed invention to the nearest prior art which could be any divalent OKT3 derived anti-CD3 antibody *lacking an Fc domain*, such as OTK3 derived $F(ab')_2$ or bivalent $(Fab'zipper)_2$.

Furthermore, it would not be clear to one of ordinary skill in the art that the OKT3 derived anti-CD3 diabody exemplified in the instant specification "exhibits a much greater immunosuppressive effect as measured by CD3 downregulation and inhibition of T cell proliferation in a mixed lymphocyte reaction than the parental antibody" as argued by applicant. This is because the CD3 down modulating abilities of the diabody and intact antibody appear to be similar and their ability to inhibit T cell proliferation in a mixed lymphocyte reaction (MLR) isn't comparable. In contrast to the diabody, as shown in Figure 9 of the instant specification the presence of the intact antibody in the MLR, even at the lowest concentration tested, *increases* T cell proliferation above and beyond that which occurs in the absence of any added antibody. This is likely due to the presence of Fc on the intact antibody and the interaction of Fc with FcγR-bearing cells in the MLR, a factor which would be removed if an anti-CD3 diabody were compared with the nearest prior art.

Lastly, applicant argues several teachings of Holliger teach away from the claimed invention. For example applicant points to col. 22, lines 15-16 "The diabodies may also bind simultaneously to two epitopes on the same surface…or by cross-linking the CD3 antigen so as to activate T-cells," and column 26, lines 22-23 "Unprimed T-cells can be activated through bridging of two CD3 molecules on the T-cell surface…"

However, these teachings do not teach away from the claimed invention because as described above the ability of an anti-CD3 antibody to bridge two CD3 on the T-cell surface and deliver a partial signal was known to be essential for its ability to immunomodulate the Th1/Th2 cytokine balance in favor of Th2. Moreover, it should be noted that this partial T cell signaling which induces immunomodulation is different from the kind of T cell signaling which occurs with cumulative CD3 cross-linking induced by an anti-CD3 antibody which is itself capable of being cross-linked, e.g., through binding to a ubiquitous cell surface receptor like FcγR or CD20 in B-lymphoma cancer cells.

In conclusion, when Applicant's arguments and the evidence of the instant specification are taken as a whole and weighed against the evidence supporting the *prima facie* case of

unpatentability, the instant claims, by a preponderance of evidence, remain unpatentable. See M.P.E.P. § 716.01(d).

Thus, the instant claims stand rejected as unpatentable over Smith in view of Hsu, Holliger and Chapman.

4. Claims 5 and 7 stand rejected and new claims 22 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith et al. (WO 9847531) in view of Hsu et al. (Transplantation. ii October 3, 2008) ), Holliger et al. (5,837,242) and Chapman et al. (Nat Biotechnol. 1999 Aug;17(8):780-3) as applied to claims 1, 2, 6, 13, 18-20, 21, 23 and 25 above, and further in view of Kipriyanov et al. (Protein Eng. 1997 Apr;10(4):445-53), for the reasons of record as put forth in the prior Office Action mailed October 3, 2008.

Applicant argues Kipriyanov does not cure the deficiencies of the Smith, Hsu, Holliger or Chapman references.

Applicant's arguments have been considered, but have not been found convincing, because as described above claims 1, 2, 6, 13, 18-20, 21, 23 and 25 are unpatentable over Smith, Hsu, Holliger and Chapman for the reasons of record, and applicant has not convincingly argued why the further addition of Kipriyanov would not render the instant claims unpatentable as well.

In conclusion, given the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in arriving at the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Thus, the instant claims are unpatentable over Smith in view of Hsu, Holliger, Chapman and Kipriyanov.

A New Grounds of Rejection necessitated by applicant's amendment is put forth below.

2. Claims 24 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for wherein a cysteine at position H100A according to the Kabat numbering scheme of said variable domains has been changed to a serine, ***does not reasonably provide enablement for*** changing this residue to any other amino acid.

In response to the previous Office Action applicant amended claim 7 to recite that the Cys has been exchanged for a Ser consistent with enabled scope as put forth in the prior Office Action mailed October 3, 2008.

However, the instant claim has the same generic limitation which was previously rejected in claim 7 and is again rejected herewith for new claim 24 for the reasons of record put forth in

the prior Office Action mailed October 3, 2008 at page 5, 3rd paragraph - page 6, 2nd paragraph.

In particular, the instant specification further discloses that the stability of an OKT3 scFv can be increased by mutagenesis of the cysteine at position H100A according to the Kabat numbering scheme to a serine and that this substitution does not adversely affect CD3 binding (see Instant specification, paragraph bridging pages 2-3).

However, the skilled artisan would be unable to predictably change the Cys residue at position H100A to any residue other than serine and be able to predict with any reasonable degree if the resulting antibody would bind the anti-CD3 antibody to the extent required to mediate the claimed immunosuppression.

For example, Kipriyanov et al. (Protein Eng. 1997 Apr;10(4):445-53, of record) teaches on page 452, left column, 2nd paragraph that H100A lies in the middle of the OKT3 CDR-H3 antigen-combining site which generally has the greatest influence on antigen binding, that change to a hydrophobic residue could lead to a change in the CDR-H3 orientation and that "we are aware that, however that the substitution [of the Cys at H100A] might interfere with antigen binding or influence contact between the variable domains. Fortunately, the Cys to Ser mutation had no effect on antigen binding..."

Given the teachings of Kipriyanov it appears the skilled artisan would not have felt comfortable predicting which amino acid changes to H100A would be have significant effect on antigen binding. Moreover, the teachings of Kipriyanov do not support the notion that the skilled artisan would consider making and testing the remaining 18 amino acid substitutions in the context of the OKT3 scFv antibody to be a matter of simple experimentation.

Consistent with the teachings of Kipriyanov put forth above, MacCallum *et al.* (J. Mol. Biol. (1996) 262:732-745, of record), analyzed many different antibodies for interactions with antigen and state that the light and heavy chain CDR3 regions dominate, and a further uncertainty about which residues are most important in CDR-H3-antigen binding come from its length variability (paragraph bridging columns on page 733).

As a further example of the unpredictability of making changes to the sequence of an antibody is provided by Rudikoff et al. (Proc. Natl. Acad. Sci. USA, 79: 1979-1 983, March 1982, of record), who teaches that even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function. In particular, Rudikoff teaches that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function (see, for example, Abstract). Similarly, Colman P. M. (Research in Immunology, 145:33-36, 1994, of record) teaches that even a very conservative substitution may abolish binding or may have very little effect on the binding affinity (see pg. 35, top of left column and pg. 33, right column).

In conclusion, the instant claims encompass an invention of substantial breadth, and essentially call for trial and error by the skilled artisan to begin discovering how to make the claimed invention without assisting the skilled artisan in such an endeavor, which is insufficient to constitute adequate enablement.

The scope of the claims must bear a reasonable correlation with the scope of enablement. *In re Fisher*, 166 USPQ 18(CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

Undue experimentation would be required to produce the invention commensurate with the breadth of the claims based on the disclosure of the instant specification and the knowledge in the art. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

3. No claim is allowed.

4. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

   A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ZACHARY SKELDING whose telephone number is (571)272-9033. The examiner can normally be reached on Monday - Friday 8:00 a.m. - 5:00 p.m.

   If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Zachary Skelding
Examiner, Art Unit 1644

/Ram R. Shukla/
Supervisory Patent Examiner, Art Unit 1644